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Synthesis of Quaternary Carbon Centers via Hydroformylation

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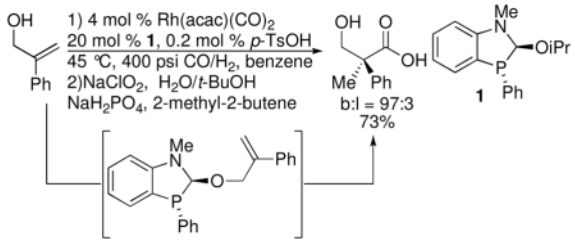
Abstract



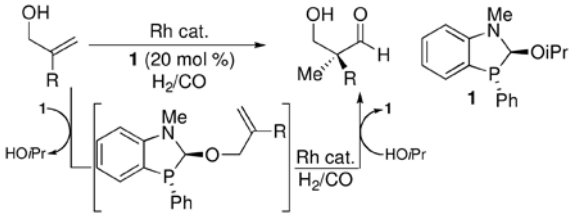
The application of hydroformylation to the synthesis of quaternary carbon centers is reported. The synthesis of the highly substituted carbon is achieved by applying a catalytic amount of **1**. Ligand **1** serves as a catalytic directing group by covalently and reversibly binding to both the substrate and catalyst. The intramolecular nature of the directing group strategy accelerates the hydroformylation reaction such that the reaction is performed at mild temperatures (35–55 °C) and with excellent regioselectivity (b:l > 94:6).

The application of directing groups in organic chemistry is a powerful technique for controlling regio- and stereoselectivity.[1] Often the use of directing groups leads to an increase in the rate and substrate scope of the reaction. Hydroformylation of disubstituted olefins has been a challenge due to the difficulty in controlling regioselectivity and the inherently poor reactivity of these substrates.[2] Phosphorous-based directing groups have been uniquely able to address these challenges making it possible to obtain highly regioselective reactions, while performing the reactions under mild conditions.[3] The liability of this strategy is the use of stoichiometric amounts of phosphorous-based ligands; however, recently our group[4] and the Breit group[5] have demonstrated that a catalytic amount of a directing group can be employed if the directing group reversibly and covalently links to the substrate. We have termed these catalytic directing groups “scaffolding ligands” due to their ability to bind both the substrate and catalyst simultaneously. Using this type of ligand allows for both regio- and diastereoselective hydroformylation of both mono- and disubstituted olefins.

A significant challenge that remains for the area of hydroformylation is the application towards the synthesis of quaternary carbon centers. The formation of quaternary centers in hydroformylation is so unfavourable that in 1948 Keulemans stated that “addition of the formyl group to a tertiary C atom does not occur, so that no quaternary C atoms are formed” (Keulemans’ rule).[6] Though this rule has generally been found to be true, there are a limited

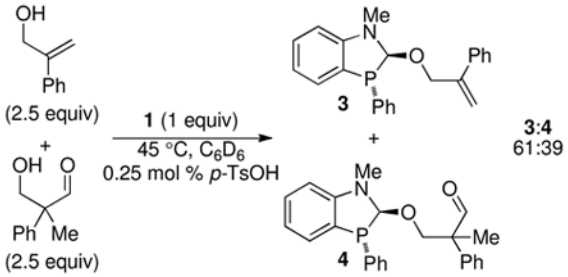
Supporting Information Available: Experimental details, exchange data between **1** and **2** as well as with the aldehyde product, compound characterization. This information is available free of charge via the Internet at http://pubs.acs.org/.

number of examples that use hydroformylation for the synthesis of quaternary carbon centers.[7,8,9,10] The majority of examples are with α, β-unsaturated esters, which are both electronically activated towards forming the branched regioisomer, and which contain an ester that can serve as a chelating group. For unactivated substrates, a sole example exists where a phosphorous directing group facilitates formation of a quaternary center from a 1,1-disubstituted olefin by hydroformylation.[3d] Inspired by this work we report that catalytic quantities of **1** can be used for the efficient generation of quaternary carbon centers (eq 1).



(1)

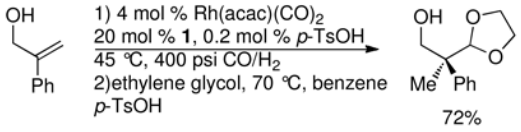
We initiated our investigation by examining the hydroformylation of **2**. Though styrenyl-based substrates are known to have a preference for the branched regioisomer,[11] α-substituted styrenes have been reported to be highly linear-selective.[12] During the course of our studies we found that the branched aldehyde product is unstable to silica gel purification, and also dimerizes to a small extent to a cyclic acetal.[13] To circumvent these problems we oxidize the unpurified reaction mixture directly and isolate the carboxylic acid product. When **2** is subjected to hydroformylation at 75 °C with PPh_3, only the linear product is formed (Table 1 entry 1). *In stark contrast when ligand 1 is used the branched product is obtained* (Table 1, entry 2). Performing a temperature screen using ligand **1**, we found that at 45 °C the branched product is formed in 61% yield and with excellent regioselectivity (b:l = 95:5, table 1, entry 3). At higher temperatures and longer reaction times a decrease in yield is observed consistent with slow product decomposition (Table 1, entry 4). Upon optimizing the pressure of CO/H_2 and reaction time the desired product could be isolated in 73% yield with b:l ratio of 97:3 (Table 1, entry 7).[14] As the CO/H_2 pressure is raised, the regioselectivity of the process increases suggesting the selectivity-determining step may be changing with pressure or higher pressure could be suppressing minor amounts of background reaction.[15] Under the same reaction conditions except using PPh_3, **2** is unreactive (Table 1, entry 8). A second control reaction was performed with the methyl ether of **2** and ligand **1** and again no reaction is observed (**Figure SI-1**). When a binding study was performed by adding 2.5 equiv of **2** and 2.5 equiv of the aldehyde product to **1**, a 61:39 ratio of **2** bound to **1** over the product bound to **1** was observed (eq 2).[16] This experiment demonstrates that there is only a slight preference for binding of **2** over the product. These results are consistent with **1** serving as a catalytic directing group that controls the regioselectivity of the reaction and accelerates the overall process.



(2)

With these initial promising results we investigated the substrate scope of the reaction. The addition of electron-withdrawing groups to the aromatic ring leads to an increase in the yields of the branched product while maintaining high selectivity (Table 2, entries 1 and 2). An electron rich aromatic ring is tolerated with a small decrease in the yield, while maintaining excellent regioselectivity (Table 2, entry 3). Aromatic rings substituted with either bromo- or chloro-groups function in the reaction (Table 2, entries 4–6). Furthermore, π-electron withdrawing groups such as nitriles and esters can be used in the reaction with b:l ratio of > 98:2 (Table 2, entries 7 and 8). Heterocyclic aromatic rings and napthylene-based substrates also yield the quaternary carbon products (Table 2, entries 9–12). Attempts to hydroformylate an *o*-tolyl substrate led to minimal conversion, suggesting that steric hindrance impedes the reaction. Using 2-methyl-propen-1-ol results in the branched product being formed as the major product (b:l = 76:24; Table 2, entry 13). We are currently investigating whether ligand modifications can be made to improve the regioselectivity for aliphatic substituted olefins.

Next, we investigated the possibility of isolating the product in the aldehyde oxidation state. This is achieved by treating the crude hydroformylation reaction mixture with ethylene glycol and catalytic *p*-TsOH to form the cyclic acetal (eq 3). Over the two steps the product was isolated in 72% yield, matching the results obtained from direct oxidation to the carboxylic acid.



(3)

We have established that using a catalytic directing group formation of quaternary carbon centers via hydroformylation can be achieved. These results demonstrate the power of directing groups to overturn inherent selectivities of reactions. The fact that these reactions are performed under mild temperatures further shows the benefits of using directing groups. We will continue to develop these scaffolding ligands and apply them to reactions that suffer from poor selectivity or reactivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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10. For an example of forming a quaternary center via hydroxymethylation of dienes see: Smejkal T, Han H, Breit B, Krische MJ. J Am Chem Soc 2009;131:10366–10367. [PubMed: 19594163]
11. For reviews of branched and enantioselective hydroformylation of styrenyl substrates see: a) Klosin J, Landis CR. Acc Chem Res 2007;40:1251–1259. [PubMed: 17997526] b) Dieguez M, Pamies O, Claver C. Tetrahedron: Asymmetry 2004;15:2113–2122. c) Agbossou F, Carpentier JF, Mortreux A. Chem Rev 1995;95:2485–2506.
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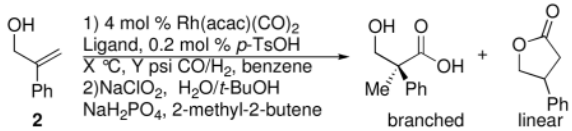
14. Ligand 1 is a racemic mixture so that the products are also formed as a racemic mixture. Future studies will investigate an enantioselective variant of this reaction.
15. Alagona and co-workers have performed calculations on the branch pathway for hydroformylation of 1,1-diphenylethene and found that all the transition states are close in energy with CO insertion, H_2 addition, or reductive elimination being rate-limiting. Ghio C, Lazzaroni R, Alagona G. Eur J Inorg Chem 2009:98–103.

16. Under the exchange conditions the aldehyde product appears to dimerize to a small degree to the cyclic acetal. Though this complicates trying to extract an equilibrium constant, we felt this most accurately reflects the conditions in which hydroformylation is occurring.

Table 1

Optimization data for hydroformylation of **2**



entry	ligand	pressure (psi)	temperature (°C)	b:l[a]	yield[b] (%)
1	PPh_3[c]	400	75	< 2:98	66[e]
2	**1**[d]	200	35	96:4	54
3	**1**[d]	200	45	95:5	61
4	**1**[d]	200	55	95:5	50
5	**1**[d]	50	45	89:11	38
6	**1**[d]	100	45	94:6	53
7	**1**[d]	400	45	97:3	70 (73)[f]
8	PPh_3[c]	400	45	-	0

[a] regioselectivities determined by ^{1}H NMR of crude reaction mixtures

[b] yields of the branched product determined by ^{1}H NMR by comparison to internal standard

[c] 8 mol % PPh_3

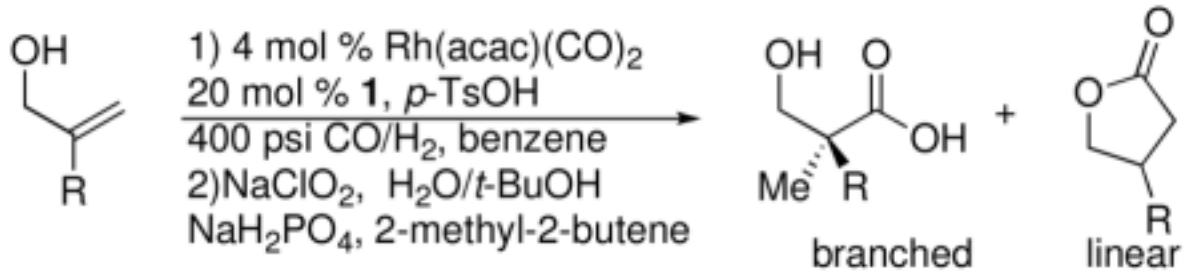
[d] 20 mol % **1**

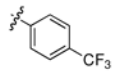
[e] isolated yield of lactone

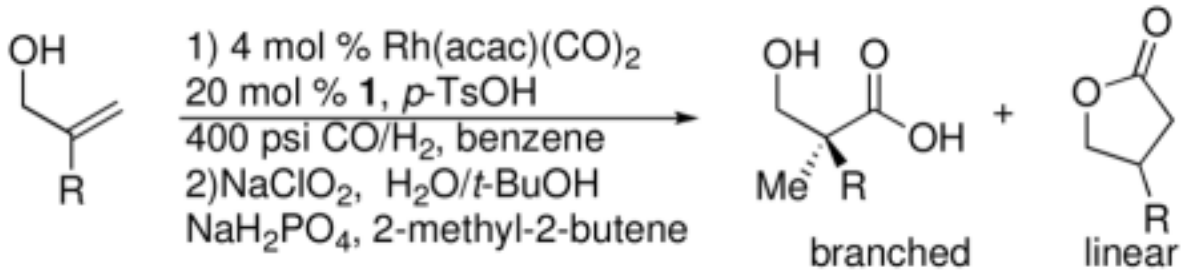
[f] isolated yield of branched product.

Table 2

Substrate Scope



entry	R	Temp (°C)	*p*-TsOH (mol %)	b:l[a]	yield (%)[b]
1		45	0.2	96:4	85



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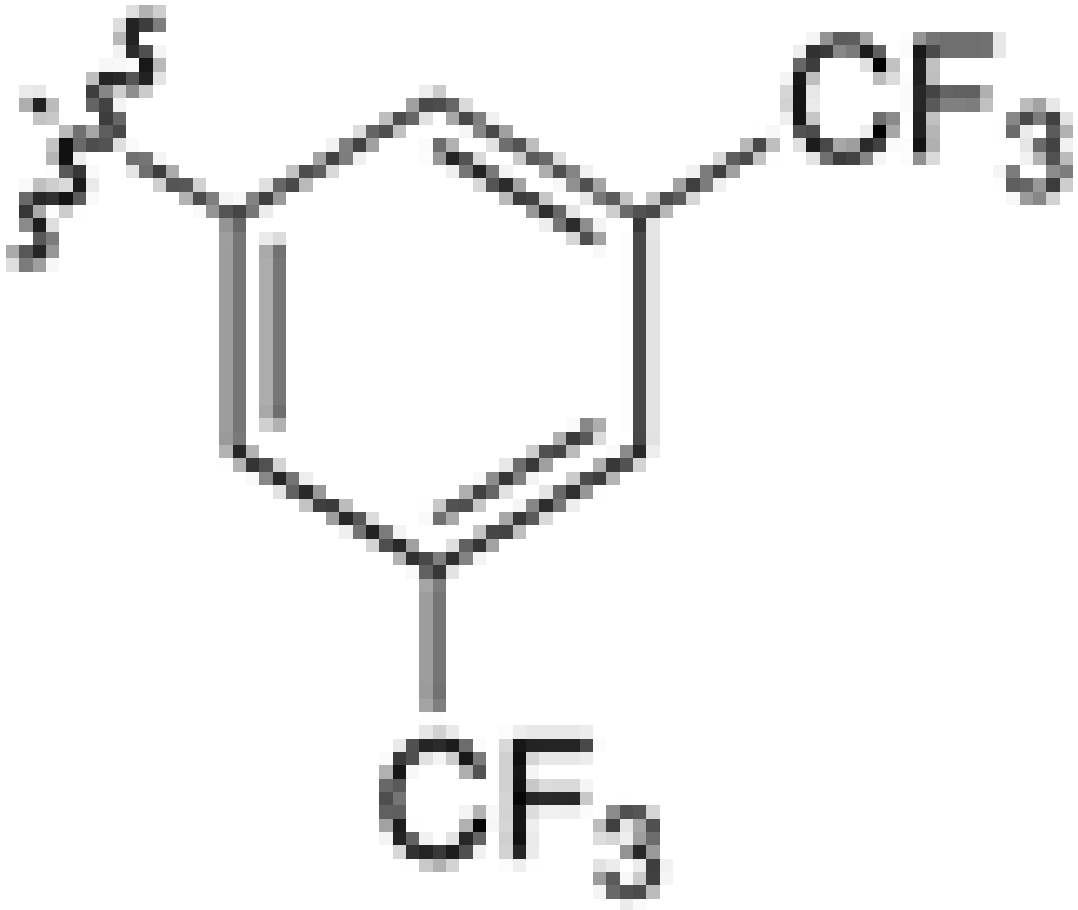
2		45	0.2	>98:2	80

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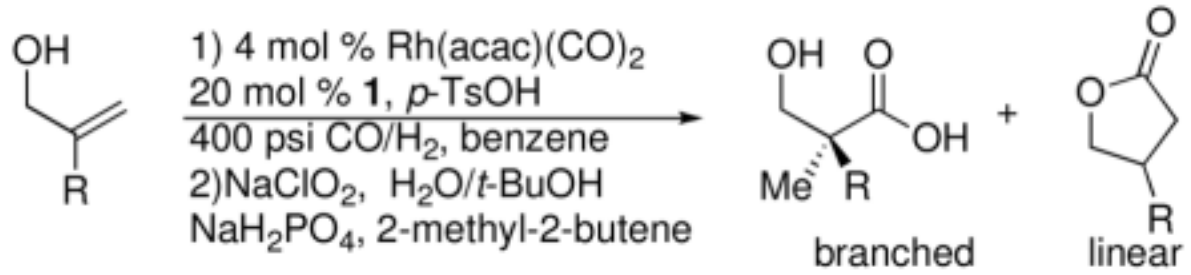
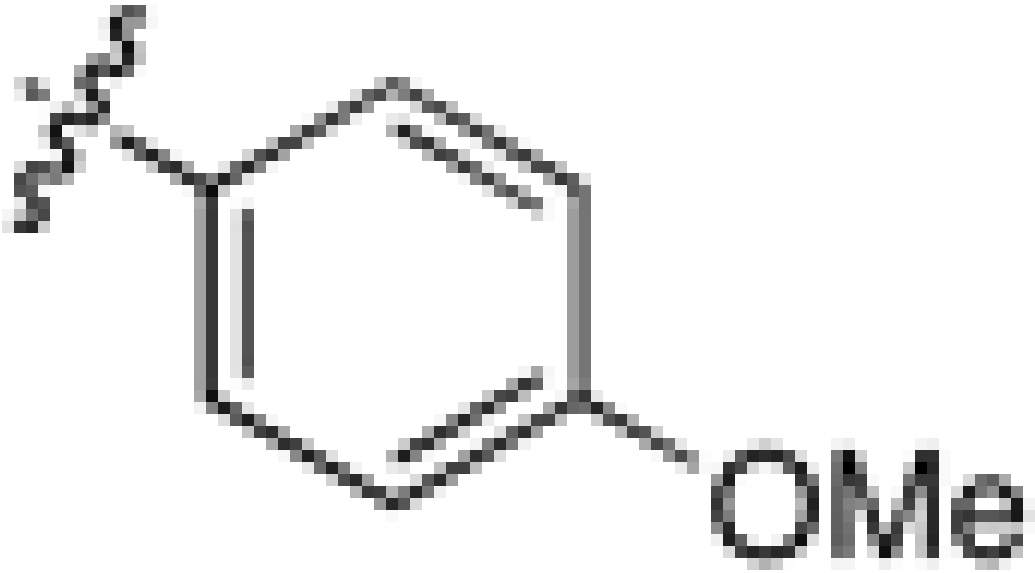


entry	R	Temp (°C)	*p*-TsOH (mol %)	b:l[a]	yield (%)[b]
3		35	0.05	>98:2	66

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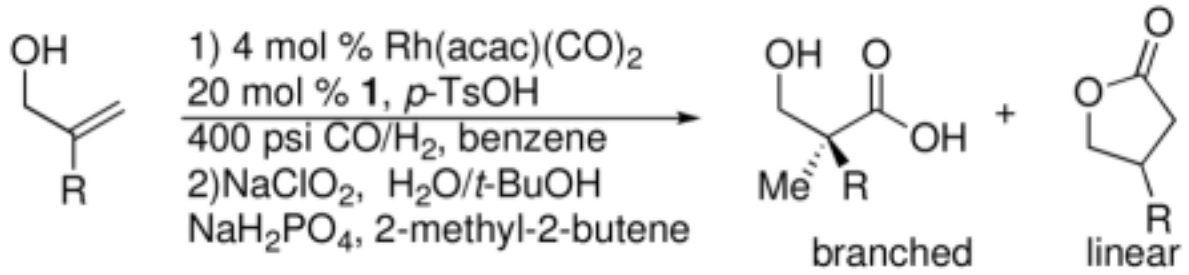

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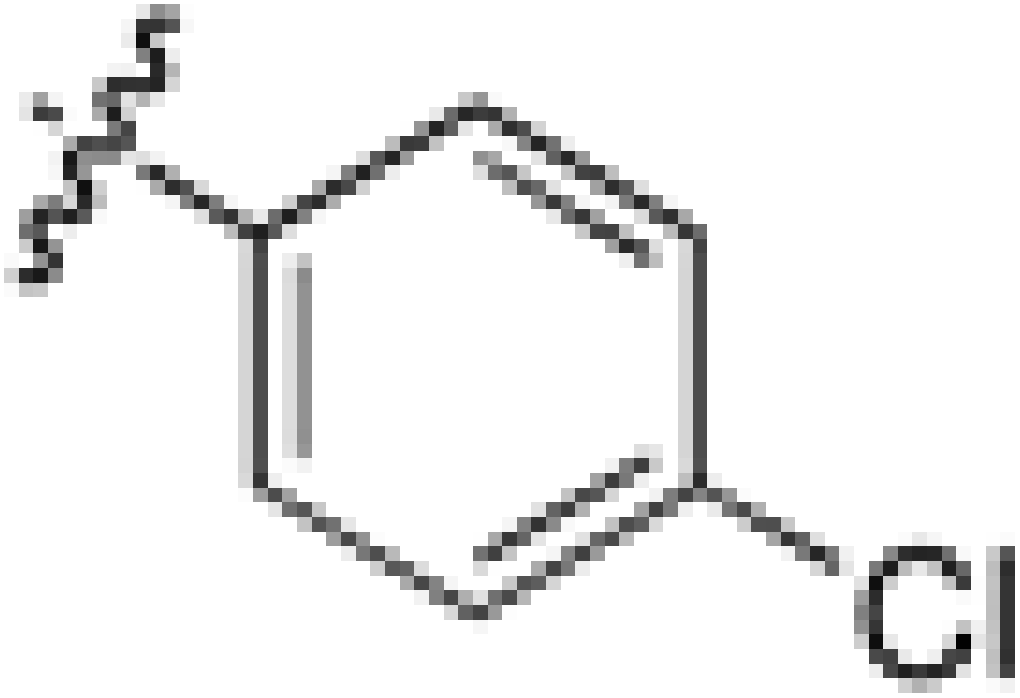
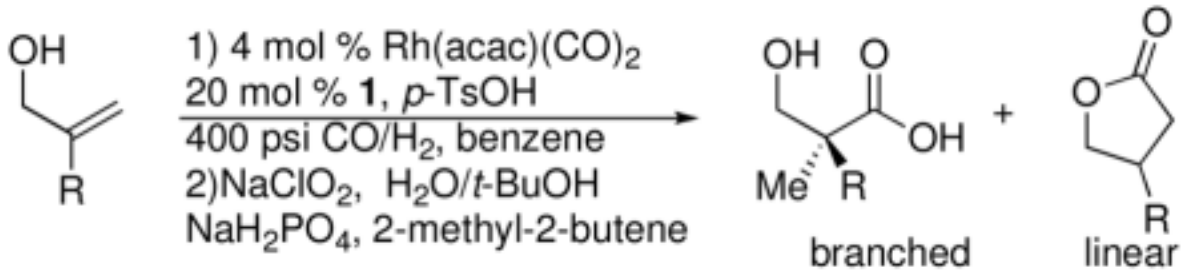
4		35	0.2	97:3	60



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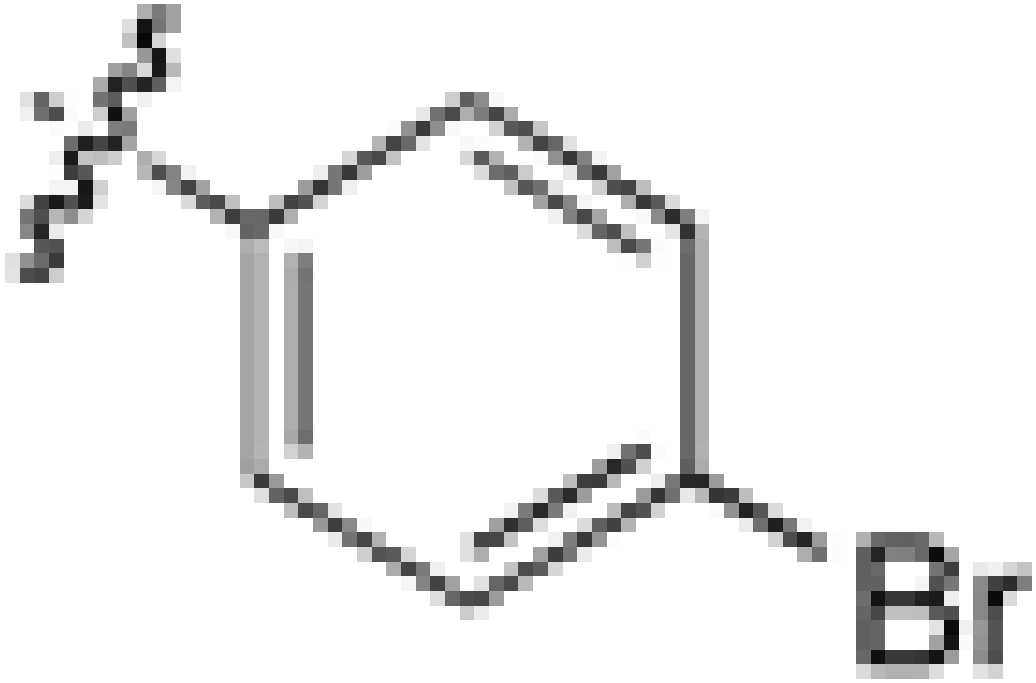
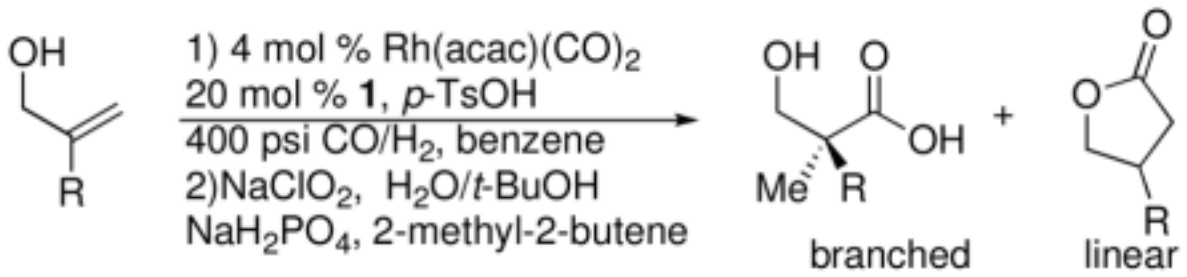
5		35	0.05	94:6	71



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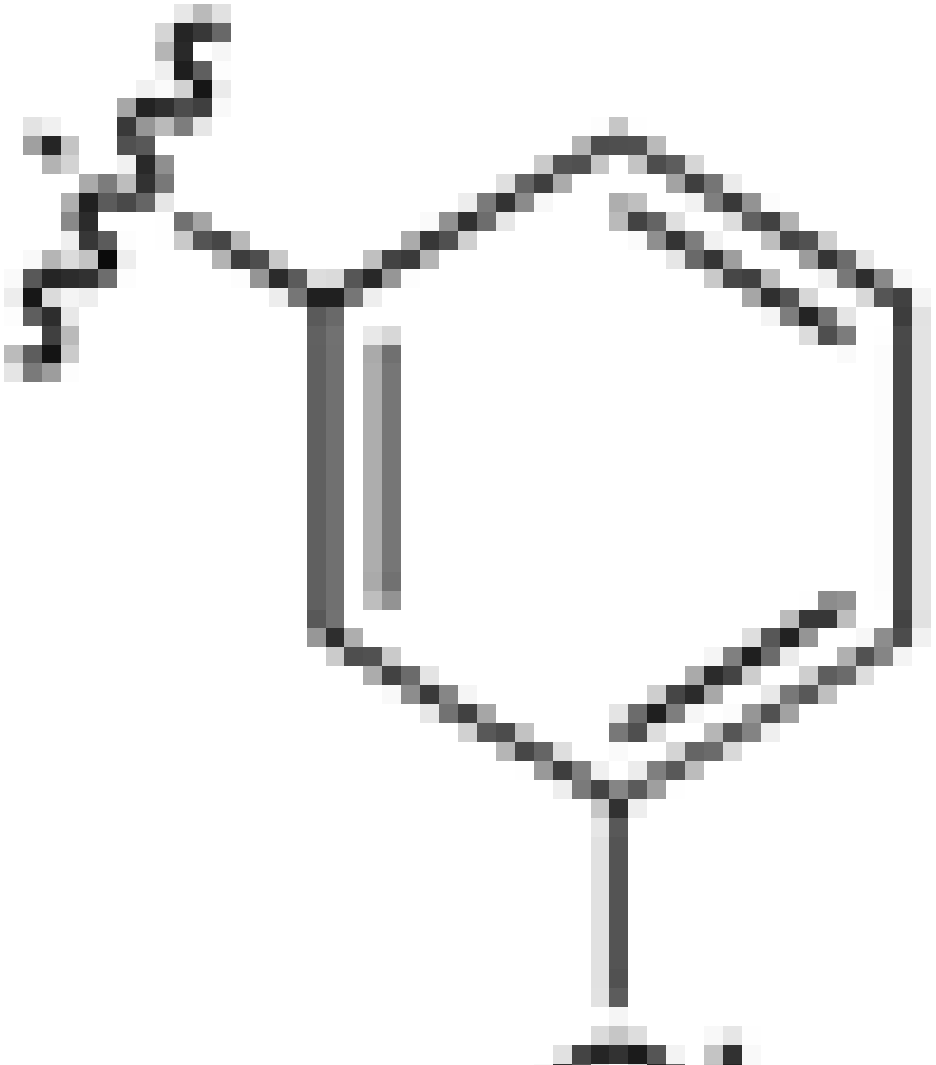
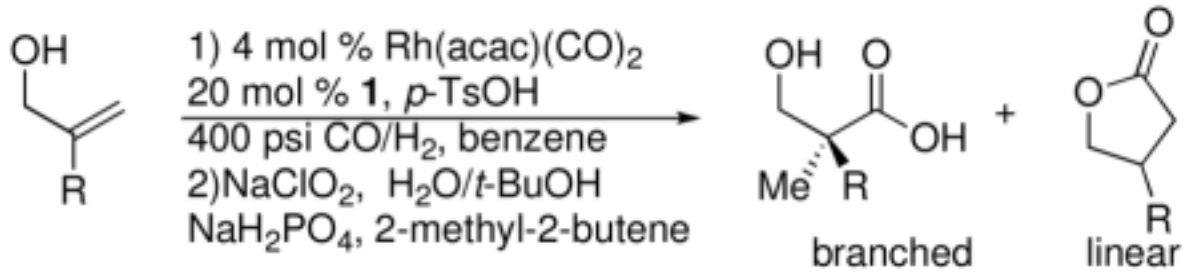
6		35	0.2	>98:2	77



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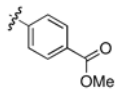
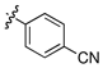
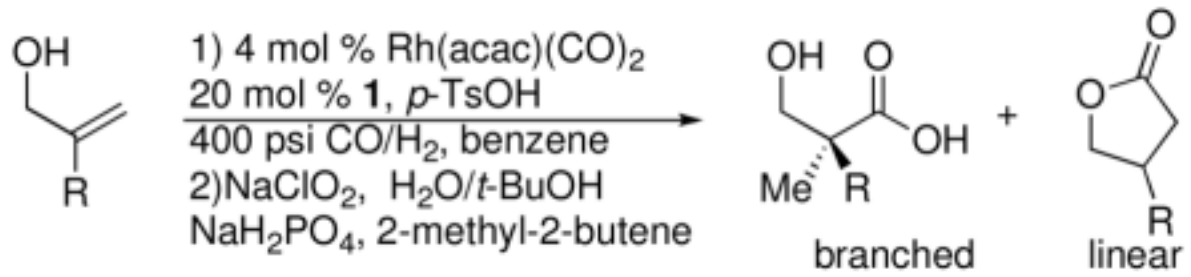
7		45	0.05	>98:2	74
8		45	0.2	>98:2	67
9		35	0.05	95:5	85



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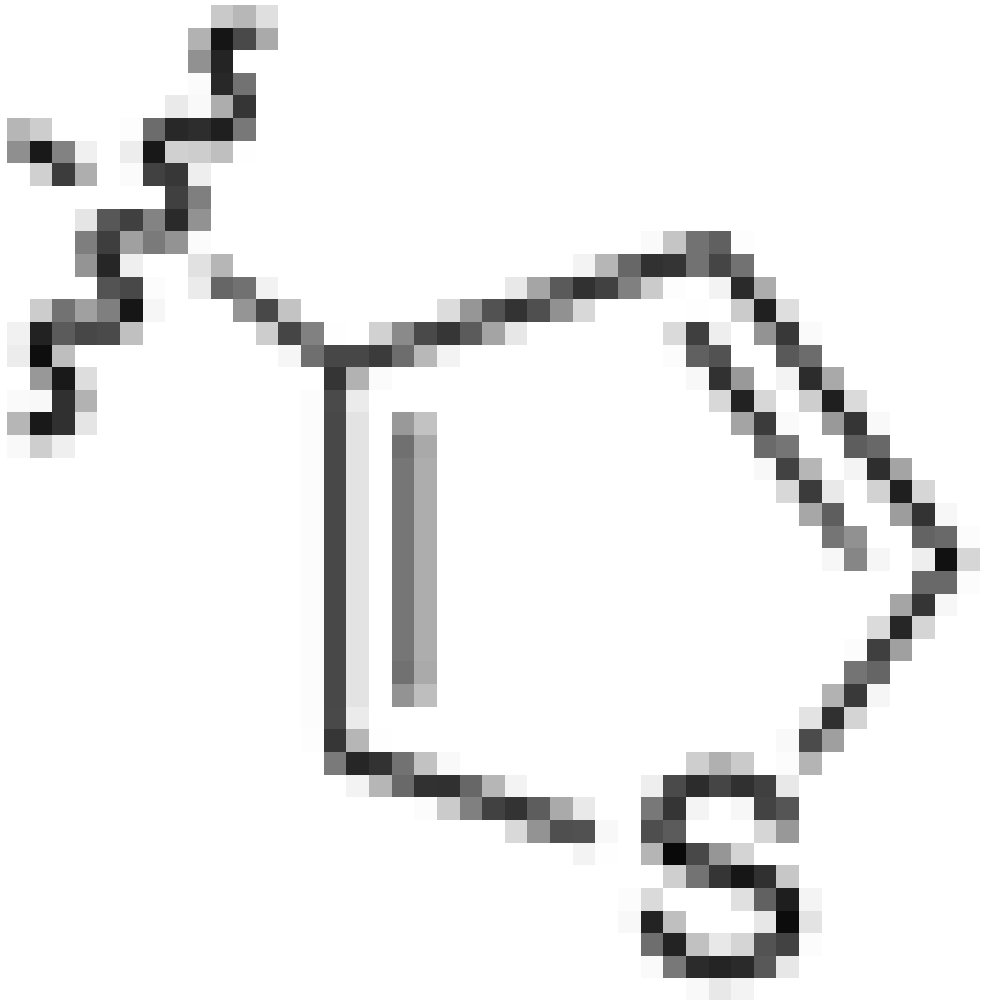

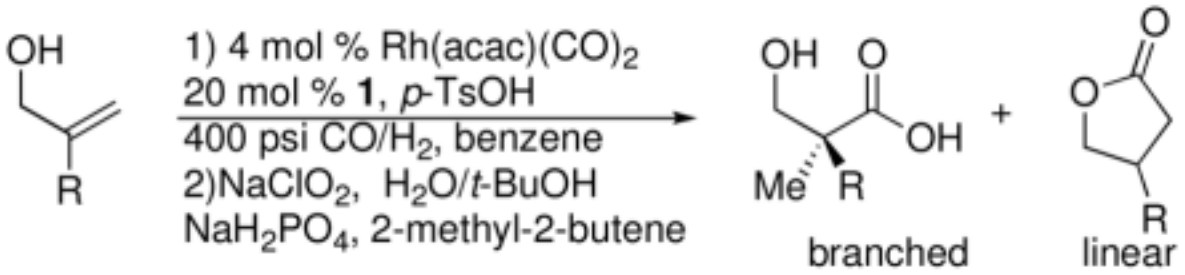

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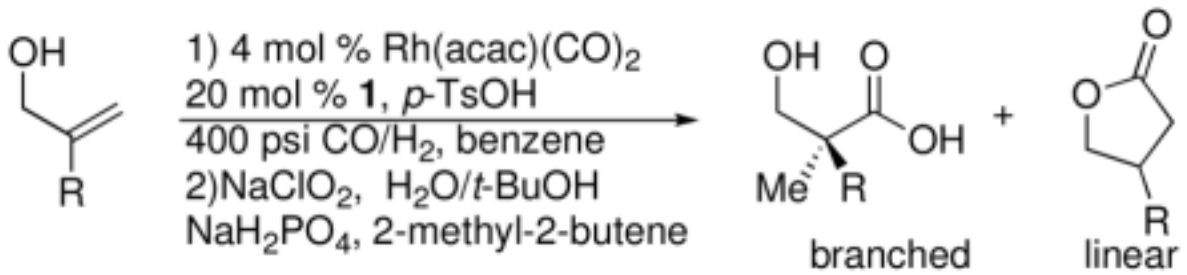
11		45	0.2	98:2	68[c]



entry	R	Temp (°C)	*p*-TsOH (mol %)	b:l[a]	yield (%)[b]
12		55	0.05	>98:2	64[c]
13		45	0.2	76:24	49

[a] regioselectivities determined by ^{1}H NMR of crude reaction mixture

[b] isolated yield of branched product.

[c] Reduction to the diol with $NaBH_4$ was performed instead of oxidation.

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